



Amikacin Pharmacokinetics To Optimize Dosing in Neonates with Perinatal Asphyxia Treated with Hypothermia

Sinziana Cristea,^a Anne Smits,^{b,c} Aida Kulo,^d Catherijne A. J. Knibbe,^{a,e}
Mirjam van Weissenbruch,^b Elke H. J. Krekels,^a Karel Allegaert^{f,g}

Division of Pharmacology, Leiden Academic Centre of Drug Research, Leiden University, Leiden, The Netherlands^a; Neonatal Intensive Care Unit, VU University Medical Center Amsterdam, Amsterdam, The Netherlands^b; Neonatal Intensive Care Unit, University Hospitals Leuven, Leuven, Belgium^c; Institute of Pharmacology, Clinical Pharmacology and Toxicology, Medical Faculty, University of Sarajevo, Sarajevo, Bosnia and Herzegovina^d; Department of Clinical Pharmacy, St. Antonius Hospital, Nieuwegein, The Netherlands^e; Intensive Care, Department of Pediatric Surgery, and Department of Neonatology, Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands^f; Department of Development and Regeneration, KU Leuven, Leuven, Belgium^g

ABSTRACT Aminoglycoside pharmacokinetics (PK) is expected to change in neonates with perinatal asphyxia treated with therapeutic hypothermia (PATH). Several amikacin dosing guidelines have been proposed for treating neonates with (suspected) septicemia; however, none provide adjustments for cases of PATH. Therefore, we aimed to quantify the differences in amikacin PK between neonates with and without PATH to propose suitable dosing recommendations. Based on amikacin therapeutic drug monitoring data collected retrospectively from neonates with PATH, combined with a published data set, we assessed the impact of PATH on amikacin PK by using population modeling. Monte Carlo and stochastic simulations were performed to establish amikacin exposures in neonates with PATH after dosing according to the current guidelines and according to proposed model-derived dosing guidelines. Amikacin clearance was decreased 40.6% in neonates with PATH, with no changes in volume of distribution. Simulations showed that increasing the dosing interval by 12 h results in a decrease in the percentage of neonates reaching toxic trough levels (>5 mg/liter), from 40 to 76% to 14 to 25%, while still reaching efficacy targets compared to the results of current dosing regimens. Based on this study, a 12-h increase in the amikacin dosing interval in neonates with PATH is proposed to correct for the reduced clearance, yielding safe and effective exposures. As amikacin is renally excreted, further studies into other renally excreted drugs may be required, as their clearance may also be impaired.

KEYWORDS amikacin, dose optimization, hypothermia, model-informed dosing, neonates, perinatal asphyxia

Aminoglycosides are administered to treat neonates with (suspected) septicemia. Aminoglycosides display a concentration-dependent effect and are almost entirely eliminated by glomerular filtration (1). Recently, a population pharmacokinetic (PK) model-derived dosing regimen for amikacin (2) was prospectively evaluated in 579 neonates, showing predictive effective and safe amikacin exposures across the entire neonatal population (2, 3). However, for neonates diagnosed with perinatal asphyxia and treated with therapeutic hypothermia (PATH), prediction of accurate amikacin disposition remains a challenge (2). This might be due to asphyxia-induced renal impairment with or without the influence of therapeutic hypothermia, which is used as a standard-of-care treatment for moderate to severe hypoxic ischemic encephalopathy in (near) term neonates. Hypothermia reduces the basal and cerebral metabolic rates,

Received 27 June 2017 Returned for
modification 28 July 2017 Accepted 24
September 2017

Accepted manuscript posted online 9
October 2017

Citation Cristea S, Smits A, Kulo A, Knibbe CAJ, van Weissenbruch M, Krekels EHJ, Allegaert K. 2017. Amikacin pharmacokinetics to optimize dosing in neonates with perinatal asphyxia treated with hypothermia. *Antimicrob Agents Chemother* 61:e01282-17. <https://doi.org/10.1128/AAC.01282-17>.

Copyright © 2017 American Society for Microbiology. All Rights Reserved.

Address correspondence to Karel Allegaert, karel.allegaert@uzleuven.be.

S.C. and A.S. contributed equally to this article.

TABLE 1 Parameter estimates and bootstrap results of the final model compared to a previously published model

Parameter	Units	Mean (% RSE)			Bootstrap median	95% prediction interval
		Model of De Cock et al. ^a	Current model	% shrinkage		
Structural model parameters						
Clearance	Liters/h/kg	0.0493 (2.2)	0.0495 (2)		0.0497	0.048–0.052
Central volume of distribution ^b	Liters	0.833 (1.34)	0.832 (1)		0.826	0.808–0.845
Intercompartmental clearance (as a fraction of CL)	Liters/h	0.415 (12.3)	0.45 (11)		0.482	0.402–0.575
Covariates						
Hypothermic treatment (θ_{HT})	^{***c}		0.594 (9)		0.587	0.498–0.673
Birth wt (θ_{BW})	^{***c}	1.34 (2.04)	1.34 (2)		1.344	1.294–1.391
Current wt (θ_{CW})	^{***d}	0.919 (2.46)	0.926 (2)		0.923	0.884–0.960
Postnatal age (θ_{PNA})	^{***c}	0.213 (9.81)	0.22 (8)		0.222	0.198–0.255
Ibuprofen ($\theta_{ibuprofen}$)	^{***c}	0.838 (3.88)	0.838 (4)		0.836	0.779–0.894
Interindividual variability						
Clearance	CV%	30 (14.9)	32 (13)	17	0.105	0.082–0.127
Residual variability						
Additive	mg/liter	0.267 (27.2)	0.305 (24)	15	0.505	0.277–0.758
Proportional	%	0.061 (8.19)	0.0606 (8)	15	0.057	0.050–0.065

^aFrom reference 11.^bCentral volume of distribution = peripheral volume of distribution.^{c***}, $CL = \text{PopCL} \times (BW/1,750)\theta_{BW} \times (1 + PNA/2) \times \theta_{PNA} \times \theta_{ibuprofen} \times \theta_{HT}$.^{d***}, $V_1 = \text{PopV}_1 \times (CW/1,750)\theta_{CW}$.

decreases the process of excitotoxicity, and results in improved neurodevelopmental outcomes (1, 4, 5). Furthermore, it may alter pharmacologic characteristics of drugs (5, 6). Drug PK profiles depend not only on drug-specific characteristics (e.g., molecular weight, lipophilicity, etc.) but also on system-specific (physiological) characteristics of the patients (e.g., cardiac output, organ perfusion, glomerular filtration [5], etc.). The system-specific characteristics are known to be affected by the pathophysiological changes that occur during both perinatal asphyxia and hypothermia (7). This specific combination of patient-related factors impairs the elimination of aminoglycosides, as previously documented for gentamicin (8–10). Data on amikacin PK in neonates with PATH are, to our knowledge, not yet available.

The aim of the current study (AMICOOL study) was to use population PK modeling and simulation approaches to further characterize amikacin disposition in neonates by quantifying the impact of PATH on amikacin PK. Therefore, PK data collected from neonates with PATH were analyzed together with data from a large and heterogeneous group of neonates without PATH (11). The findings were used to determine suitable adjustments of the most recent amikacin dosing regimens to improve the exposure in this special population. As amikacin clearance is considered a surrogate for glomerular filtration, the results may provide guidance for other drugs undergoing renal excretion.

RESULTS

Population pharmacokinetic model. Clearance (CL) in neonates with PATH was found to be decreased 40.6% (9% relative standard error [RSE]) compared to CL in neonates without PATH.

The addition of a covariate accounting for PATH on CL led to a reduction in objective function with 73 points ($P < 0.05$) and reduced the unexplained interindividual variability on CL from 0.116 to 0.104 (10% decrease). PATH was not found to influence any of the other model parameters. The final population PK parameters and bootstrap results are summarized in Table 1.

The bootstrap analysis confirmed the precision of parameter estimates of the final model, as the bootstrap medians were very similar to the parameter estimates and within the 95% prediction interval. The goodness-of-fit (GoF) plots of the final model did not show any trends or bias which would indicate model misspecifications (Fig. 1).

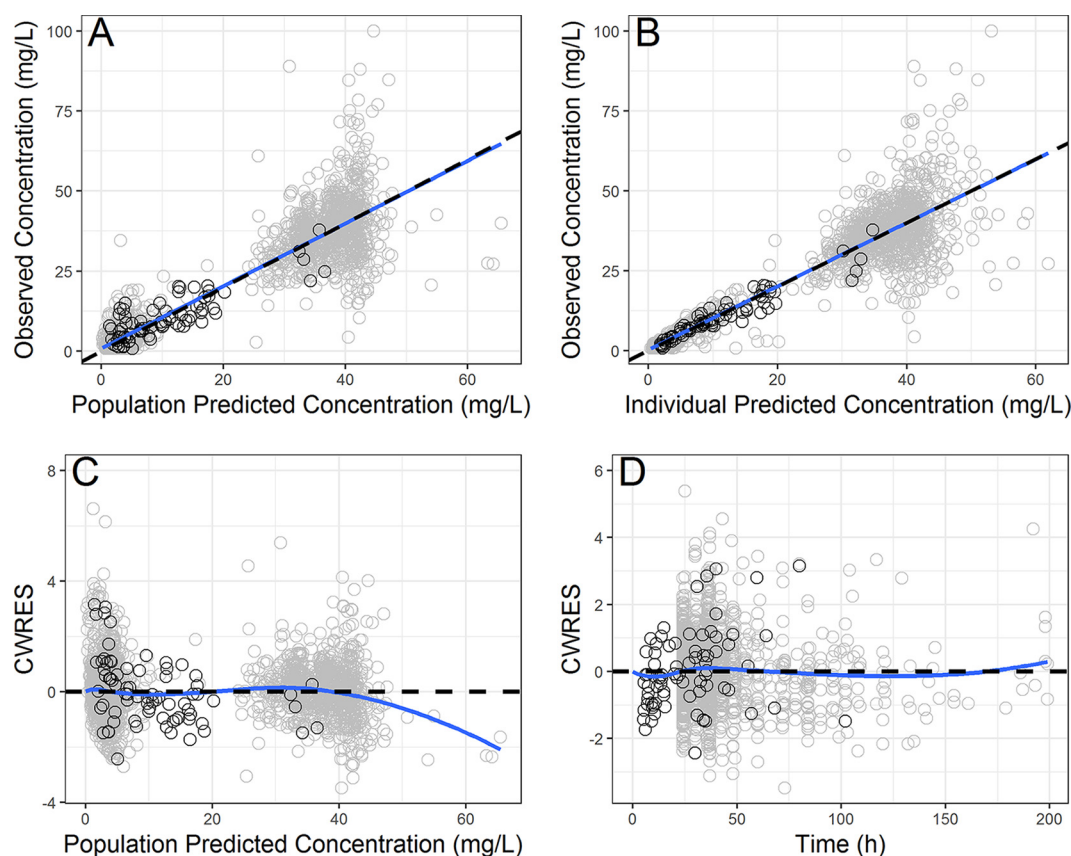


FIG 1 (A and B) Population predicted concentration (A) and individual predicted concentration (B) versus observed concentration. (C and D) Conditional weighted residuals (CWRES) versus population predicted concentration (C) and versus time after dose (D). Black circles, TDM data set (asphyxia with hypothermia); gray circles, published data set.

The normalized prediction distribution errors (NPDEs) of the predictions had a mean of 0.025, which was not significantly different from 0 ($P = 0.24$), and a standard deviation of 1.02, which was not significantly different from 1 ($P = 0.49$). Visual inspection of the results did not suggest bias in the model predictions (see Fig. S1 in the supplemental material). The NPDEs had similar distributions for both populations (with and without PATH) (Fig. S2). The condition number was 39, well below the threshold of 1,000, suggesting that the model was not overparameterized and was well supported by the data.

As the results of the PK model showed that only CL is influenced by PATH, for neonates with PATH it was proposed to use the most recently published and extensively validated dosing regimen (2), but with the dosing interval increased by 12 h, while keeping the same doses (milligrams per kilogram of body weight). The previously published and proposed dosing regimens are summarized in Table 2.

TABLE 2 Summary of analyzed dosing regimens in model-based simulations

Current wt (g) of neonate	Dosing regimen (dose, interval)			
	Original model-based dosing regimen of De Cock et al. ^a	Simplified model-based dosing regimen of Smits et al. ^b	Current dosing regimen ^b	Current dosing regimen with 12-h interval increase (proposed dosing regimen)
1,200–2,000	15 mg/kg, 36 h	15 mg/kg, 36 h	15 mg/kg, 36 h	15 mg/kg, 48 h
2,000–2,800	13 mg/kg, 30 h	15 mg/kg, 30 h	15 mg/kg, 36 h	15 mg/kg, 48 h
>2,800	12 mg/kg, 24 h	15 mg/kg, 24 h	15 mg/kg, 30 h	15 mg/kg, 42 h

^aFrom reference 11.

^bFrom reference 2.

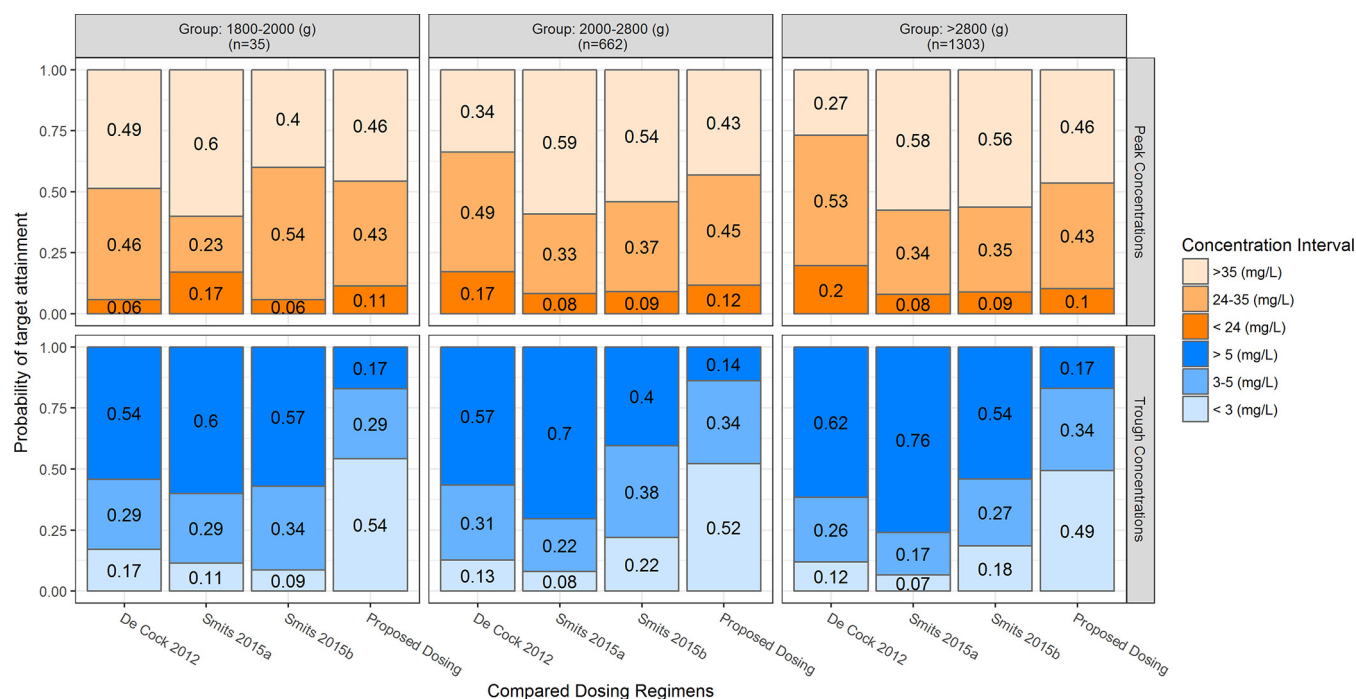


FIG 2 Stacked bar plots for Monte Carlo simulations ($n = 2,500$), presenting results for target peak (upper panels) and trough (lower panels) concentration attainment after the second amikacin dose. Results are split by the three weight groups according to which the doses were calculated (Table 2). In each panel, the three columns on the left show the results obtained with the closely related and previously published dosing regimens (2, 13), whereas the column on the right shows the results for the newly proposed dosing regimen. All simulations were performed for neonates with PATH.

MC and stochastic (SC) simulations. The results of Monte Carlo (MC) simulations upon dosing according to the three closely related dosing regimens (2, 11) for amikacin and the proposed regimen for PATH are shown in Fig. 2. In the figure, percentages of peak and trough concentrations within predefined target concentration ranges for neonates with PATH are shown, split by the three weight groups used for dosing (Table 2). Results obtained upon the second amikacin dose are presented, as the target body temperature for hypothermia is mostly achieved by then.

Figure 2 illustrates that the regimens currently used in clinical practice reached trough concentrations of >5 mg/liter in 40% to 76% of neonates, whereas with the proposed regimen with the dosing interval increased by 12 h, this percentage was reduced to 14 to 17%. Peak concentrations were below the lower efficacy threshold in only 10 to 12% of the cases, which is in accordance with the results for the published dosing regimens, for which the range was 6 to 17%.

Figure 3 comprises the results of the SC simulations and shows how the proposed regimen performed for neonates representative of our sample, with specific demographic characteristics and PATH. In this figure, results are presented for the lower (5%), median, mean, and upper (95%) birth weights (BW) of the population of neonates with PATH. Compared to the published dosing regimens (2), the proposed dosing regimen, in which the dosing interval was increased by 12 h, yielded similar target concentrations for the four tested groups, i.e., 14 to 25% of neonates had trough concentrations above the toxic level, and effective peak concentrations were not reached in fewer than 12% of neonates (Fig. 3).

DISCUSSION

In the present study, we quantified the impact of PATH on amikacin CL in neonates, a potential surrogate for glomerular filtration, and translated this finding to a dosing recommendation tailored for neonates with PATH.

Our model-based approach showed that amikacin CL decreased 40.6% in neonates with PATH compared to that in neonates without this condition. The model was used

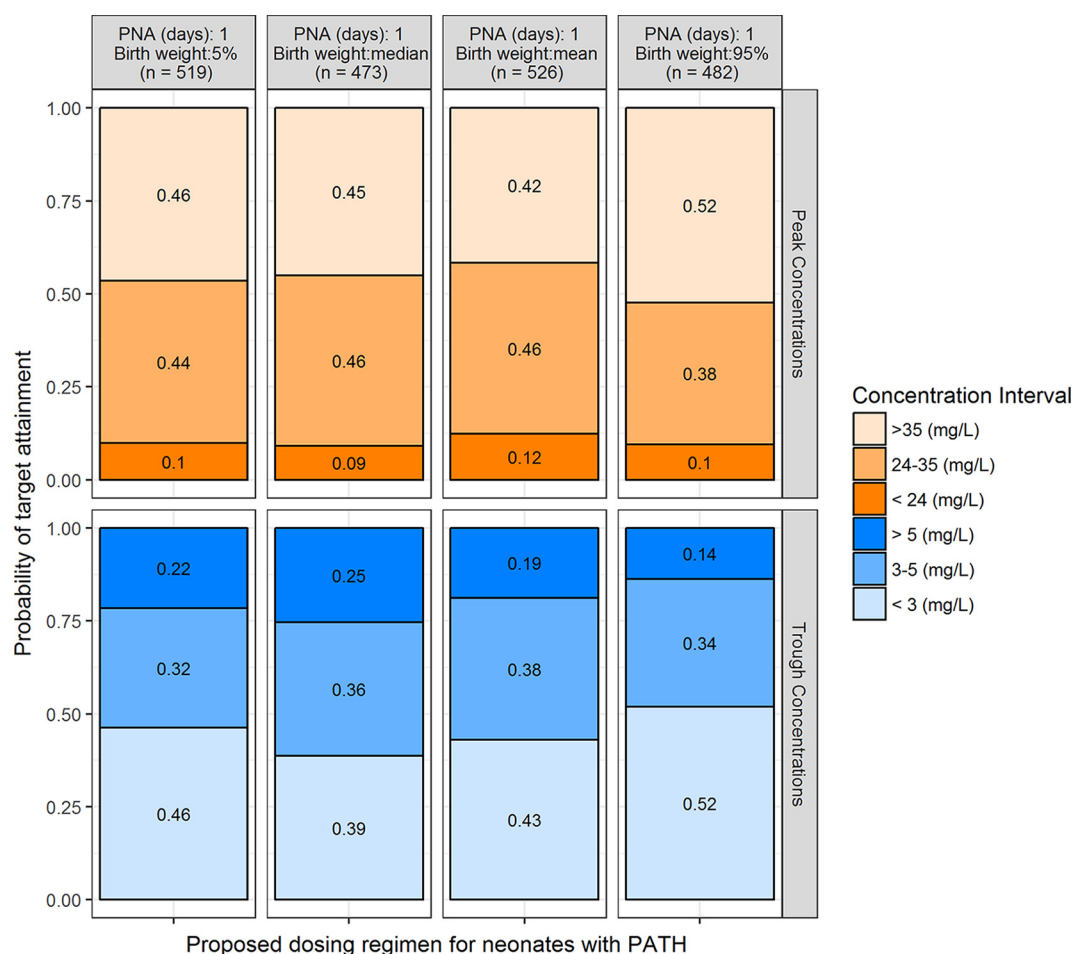


FIG 3 Stacked bar plots for stochastic simulations ($n = 2,500$), presenting results for target peak (upper panels) and trough (lower panels) concentration attainment with the model-derived dosing interval. Results obtained after the second amikacin dose are presented, with panels for the lower (5%), median, mean, and upper (95%) BW of studied neonates with PATH, at the start of the hypothermic treatment.

for simulations with targeted trough concentrations to determine an effective and practical dosing adjustment for neonates with PATH. The 12-h increase in the dosing interval of the most recent and extensively validated dosing regimen (2), while keeping the amikacin dose (milligrams per kilogram) unchanged, had a minimal impact on the peak concentrations but improved the attained trough concentrations (Fig. 2).

With the unadjusted dosing regimen, the reduced amikacin CL led to trough concentrations above the toxic threshold for a large percentage of the neonates with PATH (Fig. 2), increasing the probability of developing adverse reactions, such as nephro- and ototoxicity. Achieved peak concentrations were minimally affected by the reduced CL and increased dosing interval, as these are determined by the dose and the administration rate of the intravenous (i.v.) infusion.

The MC simulations allowed for a comparison of the performances of the published dosing regimens (2, 11) and the proposed regimen for a group of patients with demographics encountered in this group (Fig. 2), whereas the SC simulations led to a better understanding of how the proposed dosing regimen would perform in individuals with specific realistic demographic characteristics for neonates with PATH. A postnatal age (PNA) of 1 day was considered most relevant for the studied population, since hypothermic treatment is usually started within the first 6 h after birth, and the BW mean, median, and 5th and 95th percentiles were calculated for these patients for the therapeutic drug monitoring (TDM) data set (Fig. 3).

Our results showed that the proposed dosing regimen for neonates with PATH did

not impair the attainment of the amikacin treatment efficacy target, with less than 12% of the studied population reaching a suboptimal peak concentration, while the toxic effects were reduced, with less than 17% of the studied population attaining trough concentrations above 5 mg/liter (Fig. 2). This does show, nevertheless, that even with the proposed adjustment, amikacin trough TDM should still be performed as part of routine clinical care, especially for patients with PATH. It should also be noted that the validity of the traditional target concentrations for efficacy and safety of amikacin has not been established for such prolonged dosing intervals, warranting prospective evaluation of the regimen.

Although we provide the first report of amikacin PK in a dual-center cohort of neonates with PATH, other studies have been performed for other aminoglycosides (i.e., gentamicin). Frymoyer et al. (8) reported improved attainment of gentamicin target trough levels in neonates with PATH after increasing the dosing interval from 24 to 36 h (+50%). In addition, peak gentamicin concentrations were minimally affected by the increase in dosing interval. This is in concordance with our findings for amikacin and can be explained by the fact that these compounds from the same therapeutic class, eliminated by the same pathway (glomerular filtration), actually reflect the impact of perinatal asphyxia or hypothermia (or both) on the neonatal glomerular filtration rate. De Cock et al. and others previously reported that physiological maturation of amikacin CL can be used to predict the ontogeny of other compounds eliminated almost entirely by glomerular filtration (12, 13, 19). The current findings support this “semiphysiological” concept, which could be explored further to quantify the impact of perinatal asphyxia and whole-body cooling on the CL of drugs eliminated almost exclusively by glomerular filtration.

Due to the nature of the TDM data (i.e., retrospectively retrieved from patients' files, the small number of patients with PATH, and sampling during routine care), our analysis has limitations. First, we were unable to disentangle the impact of perinatal asphyxia from the impact of hypothermic treatment on amikacin CL. These are expected to have different extents, as shown in preclinical experiments in newborn pigs by Sata et al. (10) (hypoxia-ischemia) and Koren et al. (14) (hypothermia). The previous experiments also showed that the intensity of the hypothermic treatment may be relevant, as severe hypothermia (10°C temperature drop) decreased the gentamicin half-life by 36% (14), whereas mild hypothermia (4°C temperature drop) did not have an impact on CL (10). On the other hand, studies of neonates had contradicting results. While Liu et al. reported that 40% of gentamicin trough concentrations in neonates with hypoxic-ischemic encephalopathy were above the target of 2 mg/liter, they could not identify an additional impact of hypothermia on CL (15). However, Ting et al. (9) showed in neonates with hypoxic-ischemic encephalopathy that hypothermic treatment caused an increase in the half-life of gentamicin, from 7.01 h in a normothermic group to 9.57 h (+36.5%) in a hypothermic group, which suggests that the hypothermic treatment itself reduces CL as well. With this in mind, we suggest that the results of our study, including the model-derived dosing regimen, should not be extrapolated to populations other than neonates with PATH or to other drugs, even those eliminated by the same pathway, as the validity of such extrapolations requires further research.

Another limitation is the fact that at both initiation of hypothermic treatment and initiation of the rewarming phase, the body temperature of neonates is not constant. Since the numbers of samples collected during these periods were limited, it was not possible to identify a covariate relationship that reflects the dynamic changes in clearance during these periods. As a result, model-based simulations cannot be expected to be accurate for initiation of the cooling process as well as during the rewarming phase. We therefore present simulation-based results for the second amikacin dose only, as the body temperature is expected to be stable (33.5°C) throughout this interval.

To conclude, we identified a significantly decreased (40.6%) amikacin CL in (near) term neonates with PATH. Based on simulations indicating the achievement of safe trough concentrations (<5 mg/liter) while still reaching optimal peak concentrations

TABLE 3 Dosing regimens used for treatment of neonates with PATH in the UZ Leuven (Belgium) and VUmc Amsterdam (The Netherlands) NICUs

NICU	Reference for dosing regimen	Period in use	Regimen summary				
			Duration of i.v. infusion	Gestational age (wk)	wt (g)	Dose (mg/kg)	Dosing interval (h)
UZ Leuven	18	Up to July 2011	30 min	<28		20	42
				28–<31		20	36
				31–<34		18.5	30
				34–<37		17	24
				37–41		15.5	24
	11	July 2011–July 2014	20–30 min		0–800	16	48
					800–1,200	16	42
					1,200–2,000	15	36
					2,000–2,800	15	30
					≥2,800	15	24
	2	Since July 2014	20 min		0–800	16	48
					800–1,200	16	42
					1,200–2,000	15	36
					2,000–2,800	15	36
					≥2,800	15	30
VUmc Amsterdam		Up to 24 March 2015	1 h			12	24–36 ^a
		Since 24 March 2015				15	24–36 ^a

^aDetermined by TDM (see Materials and Methods).

(>24 mg/liter), we propose a 15-mg/kg dose every 42 h for children above 2,800 g and every 48 h for children between 1,800 g and 2,800 g for this special neonatal population. As a future step, this model-based dosing proposal should undergo prospective validation and eventual clinical implementation.

MATERIALS AND METHODS

Data collection. Amikacin therapeutic drug monitoring (TDM) data from routine clinical care were retrospectively collected from January 2010 to December 2015 for neonates with PATH admitted to the neonatal intensive care units (NICUs) of UZ Leuven (Belgium) and VUmc Amsterdam (The Netherlands) and receiving amikacin for (suspected) septicemia. Both centers applied the standard criteria to initiate whole-body hypothermia in term neonates (16). A total of 83 samples were retrieved, among which 75 were obtained during the hypothermic treatment period, with a median of 1.5 samples per patient (range, 1 to 3 samples per patient). Data from neonates participating in other trials (i.e., the Pharmacool trial [17]) were excluded.

The study protocols were evaluated and approved by the local institutional review boards: the UZ Leuven ethics committee approved the study protocol, and a waiver for ethical approval was obtained by VUmc Amsterdam according to the Dutch law on research with human participants.

Clinical characteristics at birth and at the time of amikacin TDM were extracted retrospectively from patients' files. Each NICU used separate dosing protocols, which are summarized in Table 3. Effective peak concentrations were considered to be within the interval of 24 to 35 mg/liter. To avoid side effects, trough concentrations were preferably below 3 mg/liter (target trough level) and strictly under 5 mg/liter (toxic trough level).

At UZ Leuven, as part of routine clinical care, amikacin TDM data were collected just before administration of the second dose. According to local clinical practice, dosing intervals could be adapted by the treating physician. At VUmc Amsterdam, the first routine amikacin TDM data were collected at least 6 h, but preferably 12 to 18 h, after the first amikacin administration. Eventual dosing adaptations were suggested by the VUmc Amsterdam pharmacy, based on the initial amikacin dose and TDM results, according to the maximum *a posteriori* Bayesian fitting method, using MW/Pharm, version 3.6 (Mediware, Groningen, The Netherlands).

Blood sample analysis. In both centers, amikacin concentrations were initially measured using a fluorescence polarization immunoassay (Abbott Tdx kit; Abbott Laboratories, Diagnostics Division, Abbott Park, IL, USA) with a lower limit of quantification (LLOQ) of 0.8 mg/liter and a coefficient of variation (CV) below 5%. From 31 May 2012, amikacin quantification at UZ Leuven was based on a kinetic interaction of microparticles in solution (KIMS) immunoassay (Roche/Hitachi Cobas c systems; Roche Diagnostics GmbH, Mannheim, Germany) with an LLOQ of 0.8 mg/liter and a CV below 4%. From September 2011, amikacin quantification at VUmc Amsterdam was based on a particle-enhanced turbidimetric inhibition immunoassay (PETINIA) (Architect c systems; Abbott, Abbott Laboratories Inc., Abbott Park, IL, USA) with an LLOQ of 2 mg/liter and a CV below 4%.

Modeling data set. TDM data from neonates with PATH were combined with a previously published data set of amikacin PK samples taken from preterm and term neonates who were not diagnosed with perinatal asphyxia and had not undergone hypothermic treatment (2, 11).

TABLE 4 Combined data set characteristics^a

Parameter	Value for data set		
	TDM data ^b	Previously published data	Combined data
No. of neonates	56	874	930
No. of samples from neonates treated with hypothermia (total no. of samples)	75 (83)	0 (2,174)	75 (2,257)
Mean (range) gestational age (wk)	38 (35–41)	31 (24–43)	32 (24–41)
Mean (range) postnatal age (days)	2 (1–4) ^c	2 (1–30)	2 (1–30)
Mean (range) birth wt (g)	3,184 (1,910–4,770)	1,530 (385–4,650)	1,795 (385–4,770)
Mean (range) current wt (g)	3,184 (1,910–4,800)	1,560 (385–4,780)	1,800 (385–4,800)
No. of neonates receiving coadministration of ibuprofen	0	118	118

^aComparison of current TDM data set with retrospectively collected data from neonates with PATH and a previously published data set (11).

^bThe cohort consisted of 13 cases from UZ Leuven and 43 cases from VUmc Amsterdam.

^cOne neonate in the TDM group did not undergo treatment with hypothermia.

The combined modeling data set consisted of data on 930 neonates, among which 55 (6%) were treated for PATH. All neonates were younger than 30 days of postnatal age (PNA), and the neonates treated with hypothermia were younger than 4 days. Characteristics of patients in the combined data set are summarized in Table 4. No outliers were identified during the current analysis.

Pharmacokinetic analysis. The PK analysis and model validation were performed using NONMEM v7.3 and PsN v3.4.2, respectively, both running under Pirana v2.9.0. The results were analyzed using R v3.3.2 running under RStudio v1.0.136.

Model development. For the structural model, a previously published population PK model on amikacin in a large and heterogeneous group of neonates (11) was used as a basis. This model consisted of a two-compartment model, with intercompartmental clearance (Q) estimated as fractions of clearance (CL) and the peripheral volume of distribution (V_2) equal to the central volume of distribution (V_1), and with a combined additive and proportional error model (11). Birth weight (BW) and PNA were covariates on CL, and current weight (CW) was a covariate on V_1 (11). In order to estimate the impact of PATH, we tested a discrete covariate on CL and V_1 . Statistical considerations were accounted for by the decrease in objective function ($-2 \log$ likelihood) value, with a significance (P) level of <0.05 (likelihood ratio test), which assumes a χ^2 distribution and the precision of parameter estimates (RSE of $<30\%$). In addition, the model fits were assessed visually using goodness-of-fit (GoF) plots split for the covariate tested.

Model validation. To assess the robustness of the parameter estimates of the final model, a nonparametric bootstrap analysis was performed in which the combined data set was resampled 1,000 times with replacement and with stratification on the origin of the data (TDM or published data). The resampled data sets were subsequently fitted with the final model, after which median and 95% confidence intervals of the obtained estimates were calculated.

To assess the predictive properties of the model, a normalized prediction distribution error (NPDE) analysis was performed using the NPDE package in R (12). Each observed concentration was compared to 1,000 simulated values for that observation.

Potential overparameterization was evaluated by calculating the condition number by taking the eigenvalues from the NONMEM output and dividing the largest one by the smallest one.

Monte Carlo and stochastic simulations. To compare the exposures that would be obtained upon dosing according to three closely related and previously published dosing regimens (2, 11) (Table 2), the final model was used to simulate peak (1 h after start of infusion) and trough (just before the subsequent dose) concentrations. For details regarding the three closely related previously published dosing regimens (Table 3), refer to the work of Smits et al. (2).

The final model was then used to determine, for neonates with PATH, an effective and practical dosing adjustment that would lead to target peak and trough concentrations. For this purpose, different doses and dosing intervals were explored to determine the regimen reaching the predefined peak and trough targets in the highest possible percentage of patients, while keeping in mind its feasibility in clinical practice. For all simulations, target peak and trough concentrations were above 24 mg/liter and below 5 mg/liter, respectively. In all simulations, neonates received two consecutive doses of a dosing regimen, assuming hypothermic treatment throughout the dosing intervals, without intermediate dose adjustments.

For both Monte Carlo (MC) simulations and stochastic (SC) simulations, the demographic characteristics (PNA, BW, CW, and gestational age) of the neonates with PATH from the TDM data set were used. For the MC simulations, 2,500 individuals were sampled, with replacement from this subpopulation, taking time-varying changes and correlations in the demographics into account. For the SC simulations, 4 neonates treated with hypothermia were generated. Each had a PNA of 1 day and a BW equal to the mean (3,093 g), median (3,000 g), 5th percentile (1,965 g), or 95th percentile (4,220 g) of the BW of the neonates with PATH from the TDM data set. For the SC simulations, for each of the 4 neonates, 2,500 individual clearance values were sampled from the frequency distribution of the clearance values obtained in the pharmacometric analysis.

SUPPLEMENTAL MATERIAL

Supplemental material for this article may be found at <https://doi.org/10.1128/AAC.01282-17>.

SUPPLEMENTAL FILE 1, PDF file, 0.3 MB.

ACKNOWLEDGMENTS

Our research activities were facilitated by the Agency for Innovation by Science and Technology in Flanders (IWT) through the SAFEPEDRUG project (IWT/SBO grant 130033). K.A. was supported by FWO Vlaanderen (senior clinical investigatorship; grant 1800209 N). C.A.J.K. received support from the Innovational Research Incentives Scheme (Vidi grant, June 2013) of the Dutch Organization for Scientific Research (NWO) for the submitted work. This work was performed within the framework of Top Institute Pharma project D2-501.

We declare that we have no conflicts of interest.

S.C. was involved in the data analysis and wrote the manuscript. A.S. was involved in conceptualizing the current study and wrote the manuscript. A.K. was involved in conceptualizing the current study and contributed to the manuscript. M.V.W. contributed to the manuscript. C.A.J.K. was involved in conceptualizing the data analysis and contributed to the manuscript. E.H.J.K. was involved in conceptualizing the data analysis and contributed to the manuscript. K.A. was principle investigator of the clinical studies, was involved in conceptualizing the current study, and contributed to the manuscript.

REFERENCES

- Ducher M, Maire P, Cerutti C, Bourhis Y, Foltz F, Sorensen P, Jelliffe R, Fauvel JP. 2001. Renal elimination of amikacin and the aging process. *Clin Pharmacokinet* 40:947. <https://doi.org/10.2165/00003088-200140120-00004>.
- Smits A, De Cock RFW, Allegaert K, Vanhaesebrouck S, Danhof M, Knibbe CAJ. 2015. Prospective evaluation of a model-based dosing regimen for amikacin in preterm and term neonates in clinical practice. *Antimicrob Agents Chemother* 59:6344–6351. <https://doi.org/10.1128/AAC.01157-15>.
- Smits A, Kulo A, van den Anker J, Allegaert K. 2017. The amikacin research program: a stepwise approach to validate dosing regimens in neonates. *Expert Opin Drug Metab Toxicol* 13:157–166. <https://doi.org/10.1080/17425255.2017.1234606>.
- Zanelli S, Buck M, Fairchild K. 2011. Physiologic and pharmacologic considerations for hypothermia therapy in neonates. *J Perinatol* 31: 377–386. <https://doi.org/10.1038/jp.2010.146>.
- Van Den Broek MPH, Groenendaal F, Egberts ACG, Rademaker CMA. 2010. Effects of hypothermia on pharmacokinetics and pharmacodynamics: a systematic review of preclinical and clinical studies. *Clin Pharmacokinet* 49:227–294. <https://doi.org/10.2165/11319360-000000000-00000>.
- Pokorna P, Wildschut E, Vobruba V, van den Anker J, Tibboel D. 2015. The impact of hypothermia on the pharmacokinetics of drugs used in neonates and young infants. *Curr Pharm Des* 21:5705–5724. <https://doi.org/10.2174/1381612821666150901110929>.
- Dammann O, Ferriero D, Gressens P. 2011. Neonatal encephalopathy or hypoxic-ischemic encephalopathy? Appropriate terminology matters. *Pediatr Res* 70:1–2. <https://doi.org/10.1203/01.pdr.0000403893.61640.b6>.
- Frymoyer A, Shirley L, Bonifacio S, Meng L, Lucas S, Guglielmo J, Sun Y, Verotta D. 2013. Every 36-hour gentamicin dosing in neonates with hypoxic ischemic encephalopathy receiving hypothermia. *J Perinatol* 33:778–782. <https://doi.org/10.1038/jp.2013.59>.
- Ting JY, Kwan E, McDougal A, Osiovich H. 2015. Pharmacokinetics of gentamicin in newborns with moderate-to-severe hypoxic-ischemic encephalopathy undergoing therapeutic hypothermia. *Indian J Pediatr* 82:119–125. <https://doi.org/10.1007/s12098-014-1527-z>.
- Satas S, Hoem NO, Melby K, Porter H, Lindgren CG, Whitelaw A, Thoresen M. 2000. Influence of mild hypothermia after hypoxia-ischemia on the pharmacokinetics of gentamicin in newborn pigs. *Biol Neonate* 77: 50–57. <https://doi.org/10.1159/000014195>.
- De Cock RFW, Allegaert K, Schreuder MF, Sherwin CMT, De Hoog M, Van Den Anker JN, Danhof M, Knibbe CA. 2012. Maturation of the glomerular filtration rate in neonates, as reflected by amikacin clearance. *Clin Pharmacokinet* 51:105–117. <https://doi.org/10.2165/11595640-000000000-00000>.
- Comets E, Brendel K, Mentré F. 2010. Model evaluation in nonlinear mixed effect models, with applications to pharmacokinetics. *J Soc Fr Stat* 151: 106–127.
- De Cock RFW, Allegaert K, Sherwin CMT, Nielsen EI, De Hoog M, Van Den Anker JN, Danhof M, Knibbe CA. 2014. A neonatal amikacin covariate model can be used to predict ontogeny of other drugs eliminated through glomerular filtration in neonates. *Pharm Res* 31:754–767. <https://doi.org/10.1007/s11095-013-1197-y>.
- Koren G, Barker C, Bohn D, Kent G, Biggar WD. 1985. Influence of hypothermia on pharmacokinetics of gentamycin and theophylline in piglets. *Crit Care Med* 13:844–847. <https://doi.org/10.1097/00003246-198510000-00014>.
- Liu X, Boroah M, Stone J, Chakkarapani E, Thoresen M. 2009. Serum gentamicin concentrations in encephalopathic infants are not affected by therapeutic hypothermia. *Pediatrics* 124:310–315. <https://doi.org/10.1542/peds.2008-2942>.
- Azzopardi DV, Strohm B, Edwards AD, Dyet L, Halliday HL, Juszczak E, Kapellou O, Levene M, Marlow N, Porter E, Thoresen M, Whitelaw A, Brocklehurst P. 2009. Moderate hypothermia to treat perinatal asphyxial encephalopathy. *N Engl J Med* 361:1349–1358. <https://doi.org/10.1056/NEJMoa0900854>.
- Bijleveld YA, de Haan TR, van der Lee HJH, Groenendaal F, Dijk PH, van Heijst A, de Jonge RCJ, Dijkman KP, van Straaten HLM, Rijken M, Zonnenberg IA, Cools F, Zecic A, Nuytemans DHGM, van Kaam AH, Mathot RAA. 2016. Altered gentamicin pharmacokinetics in term neonates undergoing controlled hypothermia. *Br J Clin Pharmacol* 81:1067–1077. <https://doi.org/10.1111/bcp.12883>.
- Langhendries JP, Battisti O, Bertrand JM, Francois A, Kalenga M, Darimont J, Scalais E, Wallemacq P. 1998. Adaptation in neonatology of the once-daily concept of aminoglycoside administration: evaluation of a dosing chart for amikacin in an intensive care unit. *Biol Neonate* 74: 351–362. <https://doi.org/10.1159/000014053>.
- Zhao W, Biran V, Jacqz-Aigrain E. 2013. Amikacin maturation model as a marker of renal maturation to predict glomerular filtration rate and vancomycin clearance in neonates. *Clin Pharmacokinet* 52:1127–1134. <https://doi.org/10.1007/s40262-013-0101-6>.